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Formulation & Evaluation of Bilayer Tablets of Sustained Release Nifedipine Layer and Immediate Release Pioglitazone Layer

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ABSTRACT

The purpose of this study was to formulate and evaluate bilayer tablets of sustained release Nifedipine layer for hypertension and Pioglitazone HCl immediate release layer for Diabetes. Direct compression method was used to formulate bilayer tablets, which contained HPMC E4M as a sustained release polymer and super disintegrating agent such as Croscarmellose sodium in different proportion from batch F1-F4. Formulation of bilayer tablets was prepared by the FP1-FP4 and FN1-FN4 powder blend of different ratios of polymer to get desirable drug release profile. Evaluation parameters of formulated bilayer tablets were hardness, friability, thickness, drug content, weight variation, and the in-vitro drug release rate pattern results indicated that the formulation F4 was the most promising formulation as the drug release from this formulation was high as compared to other formulations. In formulation F4, percentage drug release of Nifedipine sustained release layer was 98.94% at 12 hrs. and 98.89% at 60 min for Pioglitazone HCl immediate release layer.

KEYWORDS: *Nifedipine, Pioglitazone, Bilayer Tablets, Sustained Release, Immediate Release*

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INTRODUCTION

The drug Pioglitazone HCl is used to treat type-2 diabetes and Nifedipine is used to treat high blood pressure (Hypertension). Type 2 diabetes occurs when your body becomes resistant to insulin, and sugar builds up in your blood. Insulin deficiency is a symptom of type 2 diabetes, which is characterized by pancreatic-cell failure and insulin resistance in target organs. Thiazolidinediones activating PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptors, specific for PPARγ (PPAR-gamma, PPARG). Pioglitazone come under Thiazolidinediones category works by making cells more sensitive to insulin, which is used to regulate the level of glucose in the body. Improving insulin sensitivity (or reducing insulin resistance) makes it easier for sugar (glucose) in the blood to get into the cells. Hypertension is when blood pressure is too high. Narrow blood vessels, also known as arteries, create more resistance for blood flow. The narrower your arteries are, the more resistance there is, and the higher your blood pressure will be. Over the long term, the increased pressure can cause health issues, including heart disease. Calcium Channel Blockers (CCBs) are first-line treatment for primary hypertension in patients over the age of 55. Nifedipine blocks voltage gated L-type calcium channels in vascular smooth muscle and myocardial cells. Up to 75% of adults with diabetes also have hypertension so combination drug therapy reduces dose burden. These are the novel drug delivery systems where combination of two drugs in a single unit having different release profiles Immediate release Pioglitazone HCl and sustained release Nifedipine. Bilayer tablets are the medicines which consist of two same or different drugs combined in a single dose for effective treatment of the disease. Bilayer tablet has patient compliance and is beneficial for sequential release of two drugs in combination. Bilayer tablet is an advanced technology that helps in overcoming the limitations of a single-layered tablet.

Direct Compression: In which tablets formulations are directly compressed from a powder blend of suitable excipients and API is called a direct compression method. Pre-treatment of blended powder by dry or wet granulation procedure is not necessary. It provides merits mostly in terms of speedy production, as it requires less machinery, reduced number of personnel, fewer unit operations and significantly less processing time along with improved product stability.

Materials and Methods:

Pioglitazone HCl was provided by Abhilasha Pharma Pvt.Ltd and Nifedipine was provided by Suchem Laboratories Pvt.Ltd (Mumbai, India). Ashland Inc. (Netherland) provided the HPMC E4M polymer as a free sample. Fine Chem Ltd. (Mumbai, India) supplied Croscarmellose sodium, Microcrystalline cellulose (Avicel pH 102), Magnesium stearate, Talc. All of the reagents used in this experiment was analytical quality grade.

Methods

Method for Preparation of Tablets:

Direct Compression: In which tablets formulations are directly compressed from a powder blend of suitable excipients and API is called a direct compression method. Pre-treatment of blended powder by dry or wet granulation procedure is not necessary. It provides merits mostly in terms of speedy production, as it requires less machinery, reduced number of personnel, fewer unit operations and significantly less processing time along with improved product stability. In this formulation direct compression method was used.

Identification of pure drug:

Identification of pure drug was carried out by UV-Visible spectroscopy and Fourier Transform Infra-Red Spectrophotometry scanned in the range of 200-400nm.Also Identification of pure drug was carried out by Differential Scanning Calorimetry (DSC) study.

Drug-excipient compatibility study:

Studies of drug-excipient compatibility are important to ascertain drug and excipients are compatible with each other. Differential Scanning Calorimetry (DSC) study and Fourier Transform Infra-Red Spectrophotometry (FTIR) are used to study drug-excipient compatibility.

UV-Spectroscopy:

The stock solution of Pioglitazone HCl and Nifedipine was prepared in Methanol; UV spectrum of 10µg/ml solution of Pioglitazone HCl and Nifedipine was taken to determine its absorption maxima (λ max). The UV spectrum of Pioglitazone HCl was shows absorbance maximum (λ max) at 268 nm. Nifedipine's UV spectrum was obtained in methanol as a solvent, with absorption maxima at 238 nm. The linearity of the responses of both drugs was verified at 2–12 µg/ml concentrations. The calibration curve was obtained by plotting the absorbance versus the concentration data and was treated by linear regression analysis. The equation of the linearity curve for Pioglitazone HCl obtained was y = 0.0806x + 0.0089. The linearity curve was found to be linear for mentioned concentrations (the correlation coefficient (r^2) of determination was 0.9996 (Fig.1). Similarly, the equation of the linearity curve for Nifedipine obtained was y = 0.0669x+ 0.0091. The linearity curve was found to be linear for mentioned concentrations. (The correlation coefficient (r^2) of determination was 0.999)

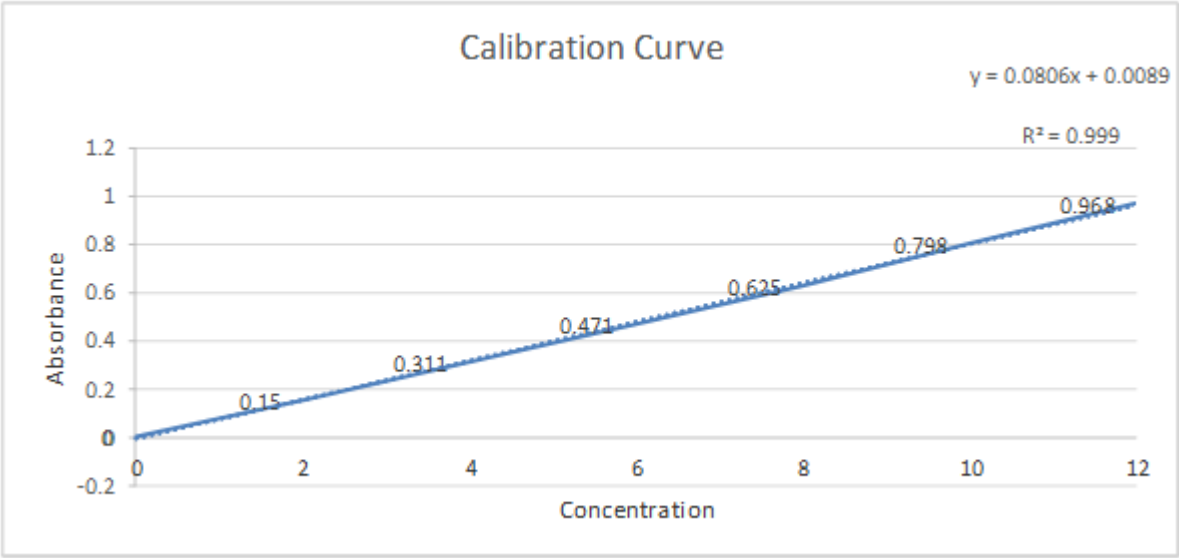

Fig 1. Calibration Graph of Pioglitazone HCl

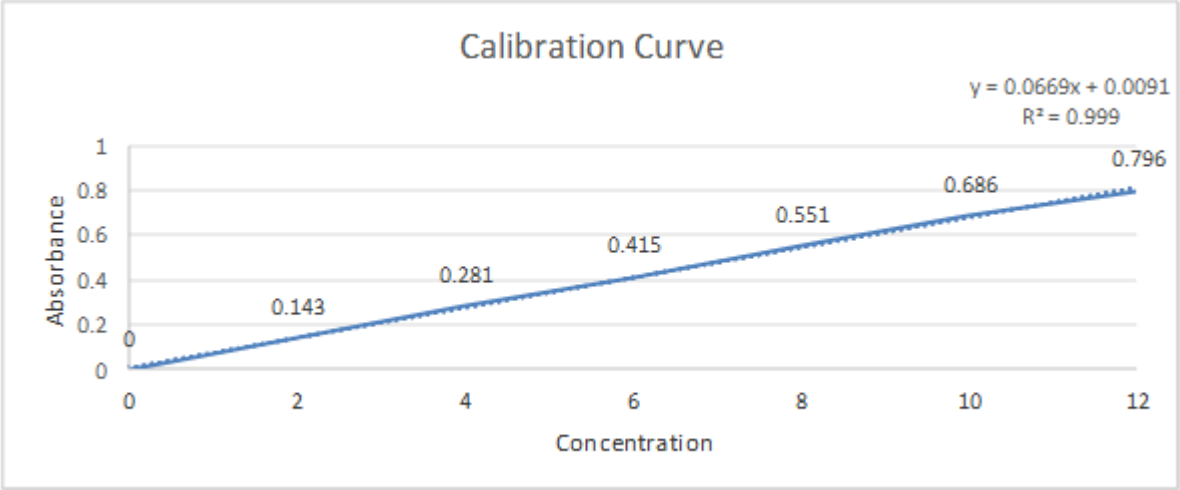

Fig 2. Calibration Graph of Nifedipine

FTIR spectroscopy:

FTIR (Shimadzu 8400s) spectrophotometer were used in the range of 400-4000 cm^{-1} using potassium bromide discs (Mixing ratio1:1) The samples were hermetically sealed in aluminium pans and heated at a constant rate of 10°C/ min over a temperature range of 40 to 300°C.

The FTIR spectrums of pure drug Pioglitazone HCl as well Nifedipine and physical mixtures of drugs and polymers were studied separately as per the excipients used in the formulation. It was observed that there were no major shifts in the main peaks of either drug. This indicates that there were no compatibility problems with the drug with the polymers and excipients used in the formulation. Pioglitazone HCl had peaks at 3410 (N-H stretching), 3255 (O-H stretching), 1319 (C-N stretching), and 1689 (C=O stretching), 663 (C-S stretching),1242 (C-O stretching) **(Fig.3),** while Nifedipine showed characteristic peak values at 3333 (C-H stretching); 2955 (Aromatic C-H stretching); 1681 (C=O stretching) and 1435 (OH stretching),1225(C-O stretching),748(N-O stretching) **(Fig.4).** These peak values were in accordance with standard reported spectra of Pioglitazone HCl and Nifedipine.

Also, there was no indication of an interaction between Pioglitazone HCl and Croscarmellose Sodium Mix, **(Fig.5)** according to the findings. IR spectra the combined peak of drug and excipient shows no change or slight change from the standard value from this study concluded that the given mixture is compatible with each other. IR spectrum of physical mixture of Nifedipine and HPMC E4M Mix **(Fig.6)** is showed combined peak of drug and excipient no change or slightly change from the standard value. From this study concluded that the given physical mixture of Nifedipine and HPMC E4M Mix is compatible with each other.

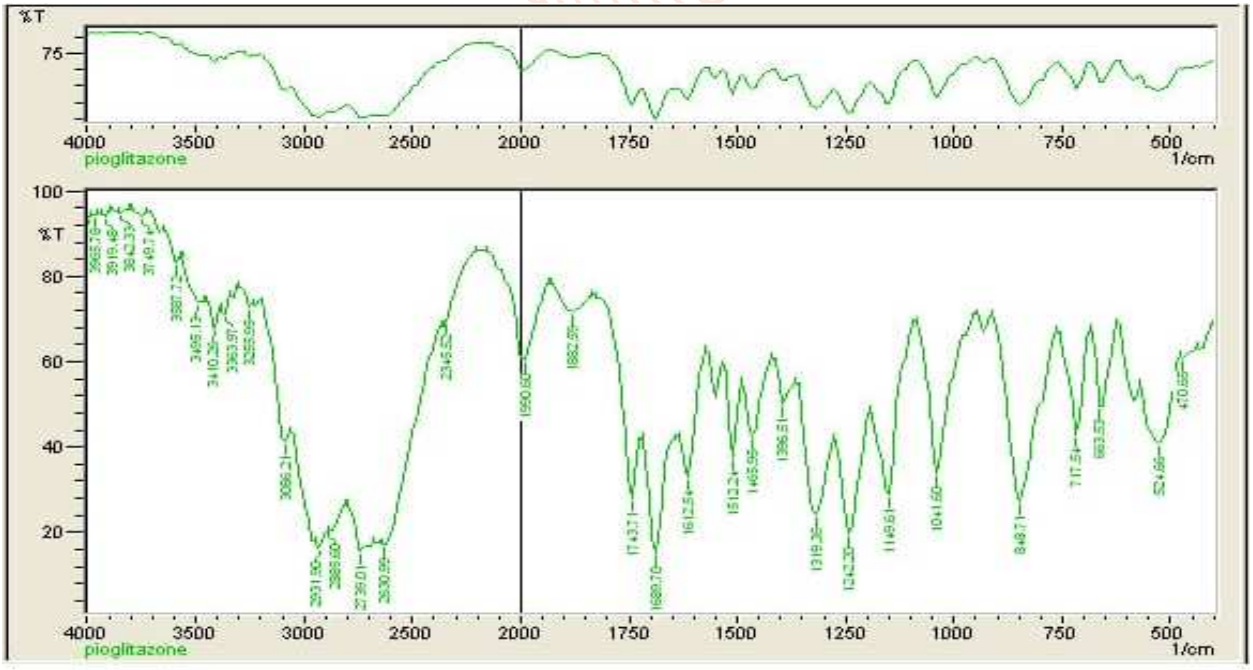

Fig.3 IR Spectra of Pioglitazone HCl

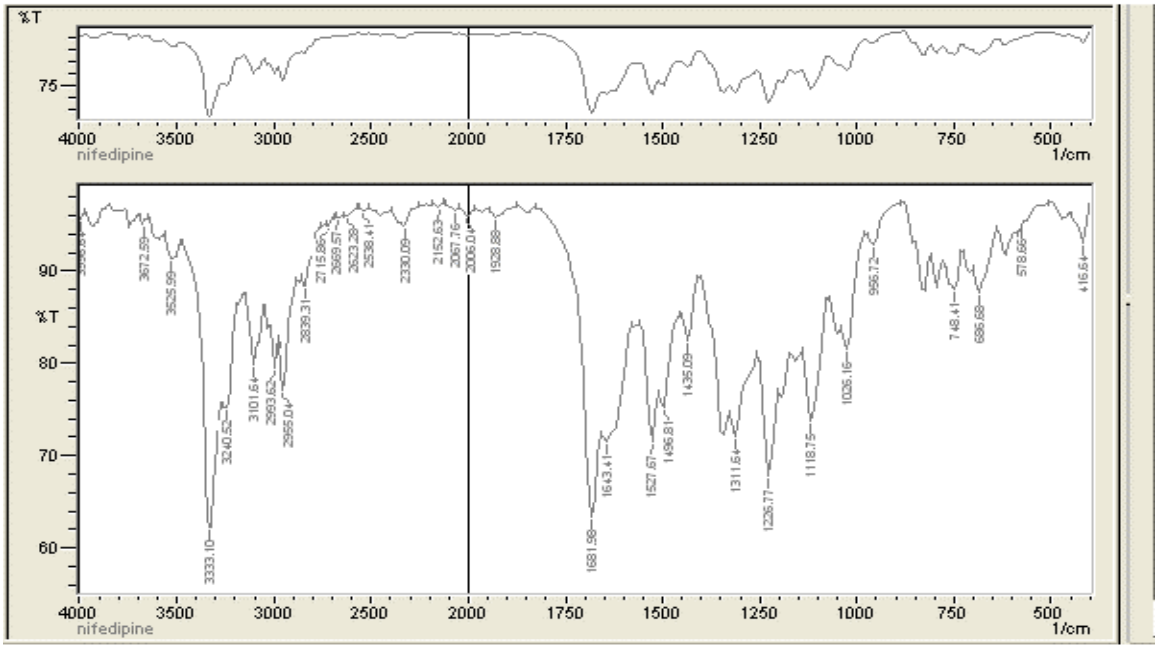

Fig.4 IR Spectrum of Nifedipine

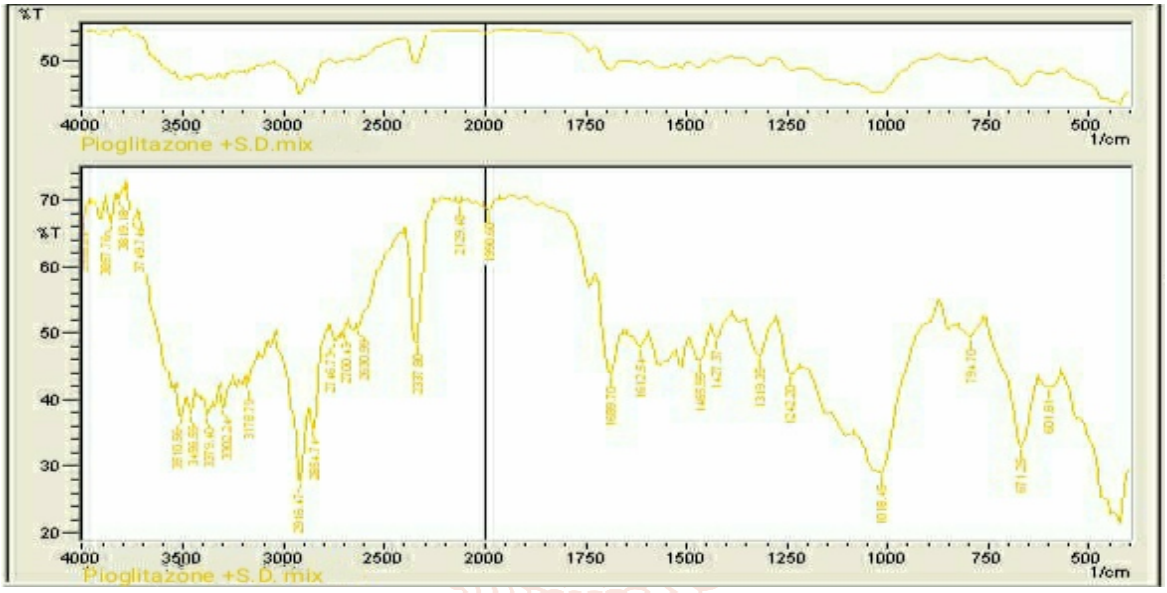

Fig.5 IR spectra of Pioglitazone + Croscarmellose Sodium and other excipients

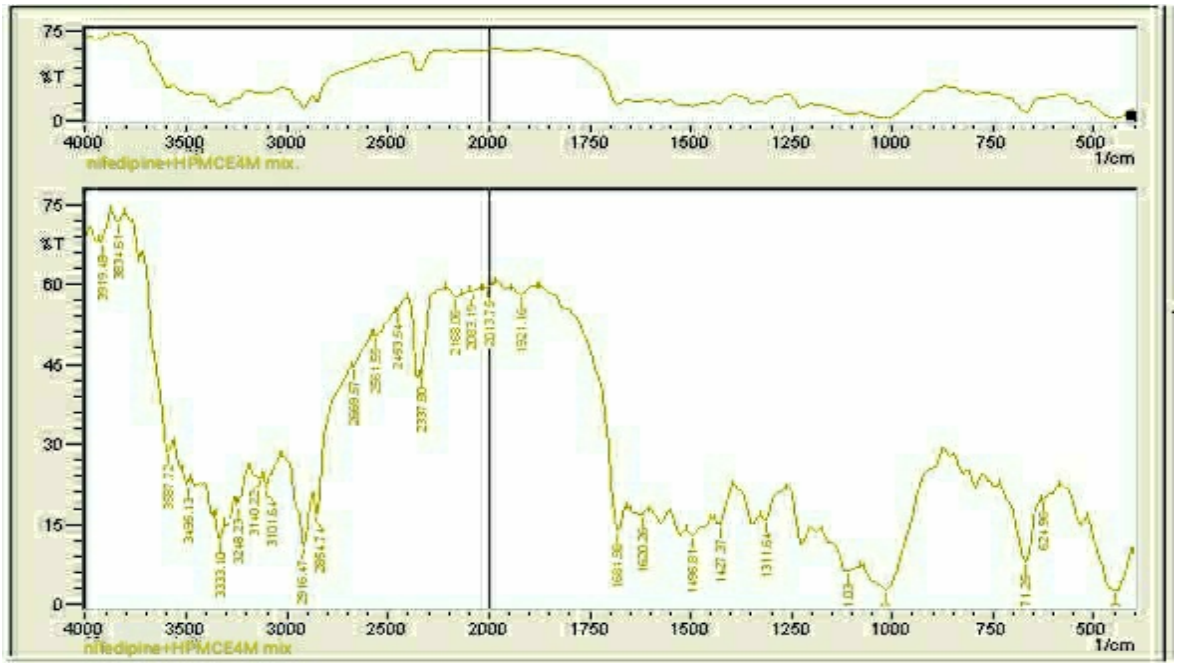

Fig.6 IR spectra of Nifedipine + HPMC E4 M Mix

Differential Scanning Calorimetry (DSC) study:

Mettle Toledo (*SW920) Differential Scanning Calorimeter using aluminum pans equipped with an intracooler and a refrigerated cooling system was used to analyses the thermal behavior of Pioglitazone HCl and Nifedipine, Indian standard was used to calibrate the DSC temperature. The thermal behavior of hermetically sealed samples heated at 10˚C/min.

DSC Thermogram of Pioglitazone HCl is shown in **Figure 10.7** Thermogram indicates a sharp endotherm at 190°C, which is corresponding to the melting point of Pioglitazone HCl. From this it is conclude that the given sample of Pioglitazone HCl is in pure form.

Figure 10.8 shows the DSC curve of pure Nifedipine, which has a distinctive abrupt endothermic peak at 169.76 0 C, showing the drug's melting point. According to the findings of the drug authentication research, the sample of Nifedipine is pure and meets Indian pharmacopeial requirements.

Compatibility studies were performed in order to confirm the drug-excipient compatibility. The physical mixtures of Pioglitazone HCl +Croscarmellose Sodium, Nifedipine + HPMC E4M were taken as 1:1 ratio

DSC Thermogram of given sample of Pioglitazone HCl **+**Croscarmellose Sodium and other excipients is shown in **Figure 9.** Thermogram indicates a sharp endotherm at 180°C, which is corresponding to the melting point of Pioglitazone HCl. From this it is conclude that the given sample of Pioglitazone HCl+ Croscarmellose Sodium and other excipients is compatible with each other.

DSC Thermogram of given sample of Nifedipine + HPMC E4M and other excipients is shown in **Figure 10.** Thermogram indicates a sharp endotherm at 174°C, which is corresponding to the melting point of Nifedipine. From this it is conclude that the given sample of Nifedipine + HPMC E4M and other excipients is compatible.

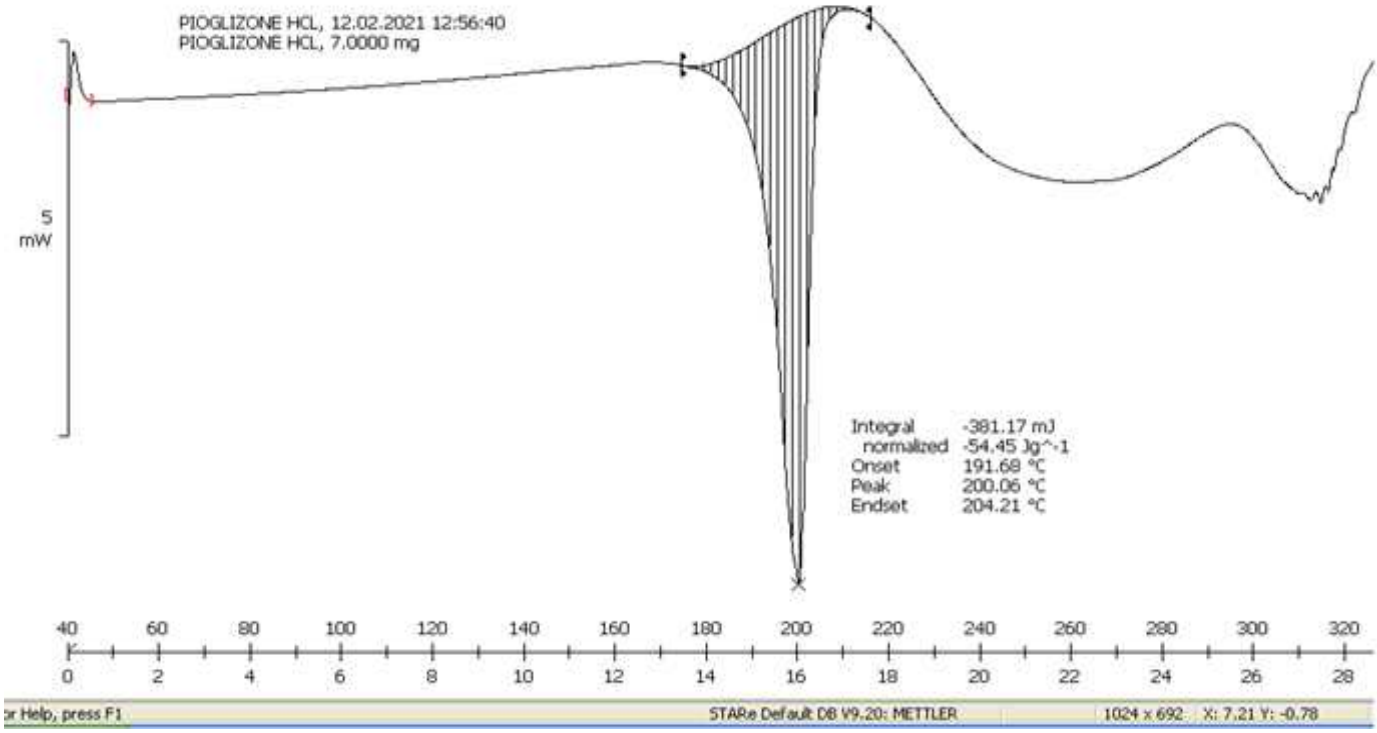

Fig.7 DSC Thermogram of Pioglitazone HCl

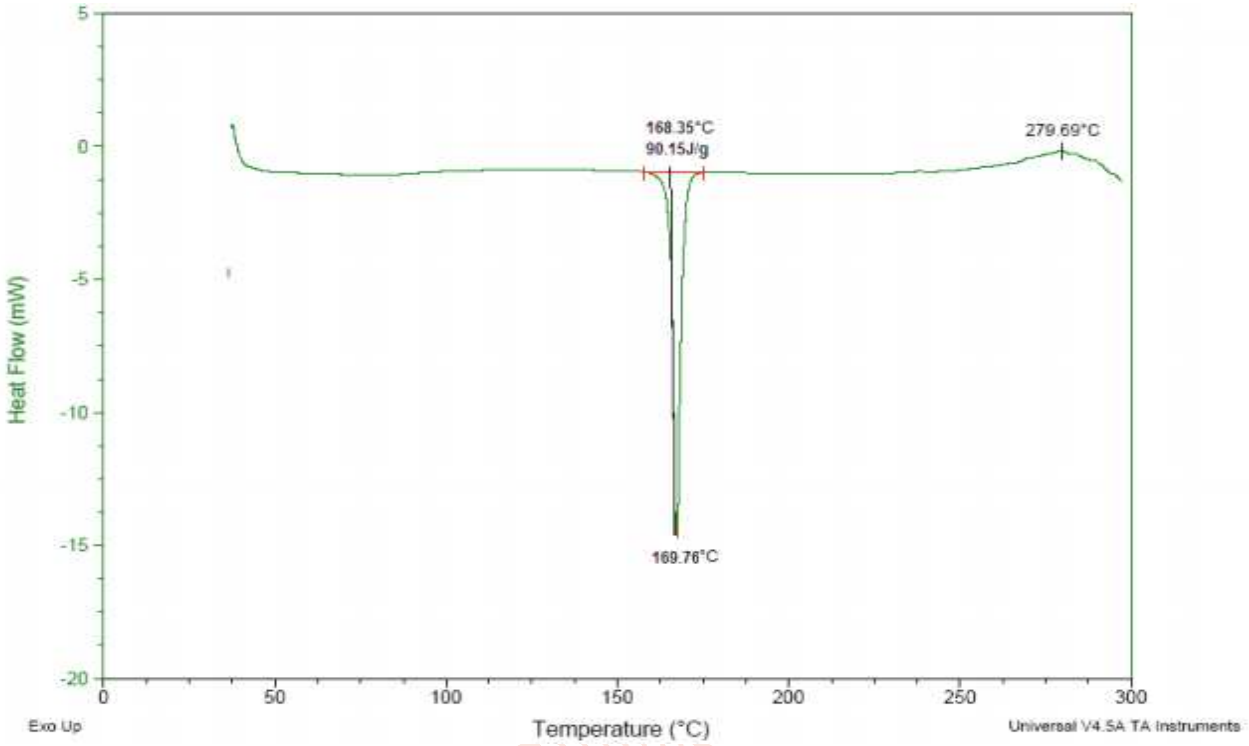

Fig.8 DSC Thermogram of Nifedipine

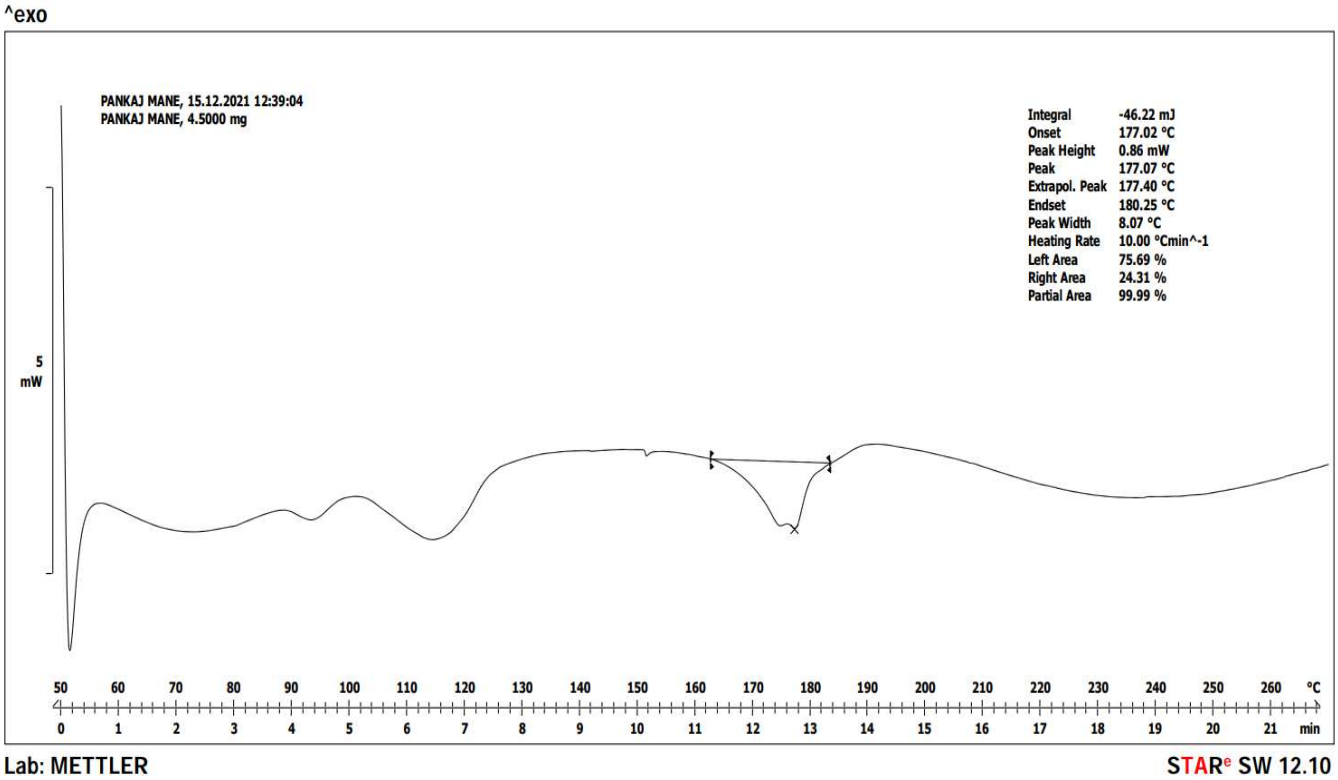

Fig.9 DSC Thermogram of Pioglitazone HCl+ Croscarmellose Sodium and other excipients

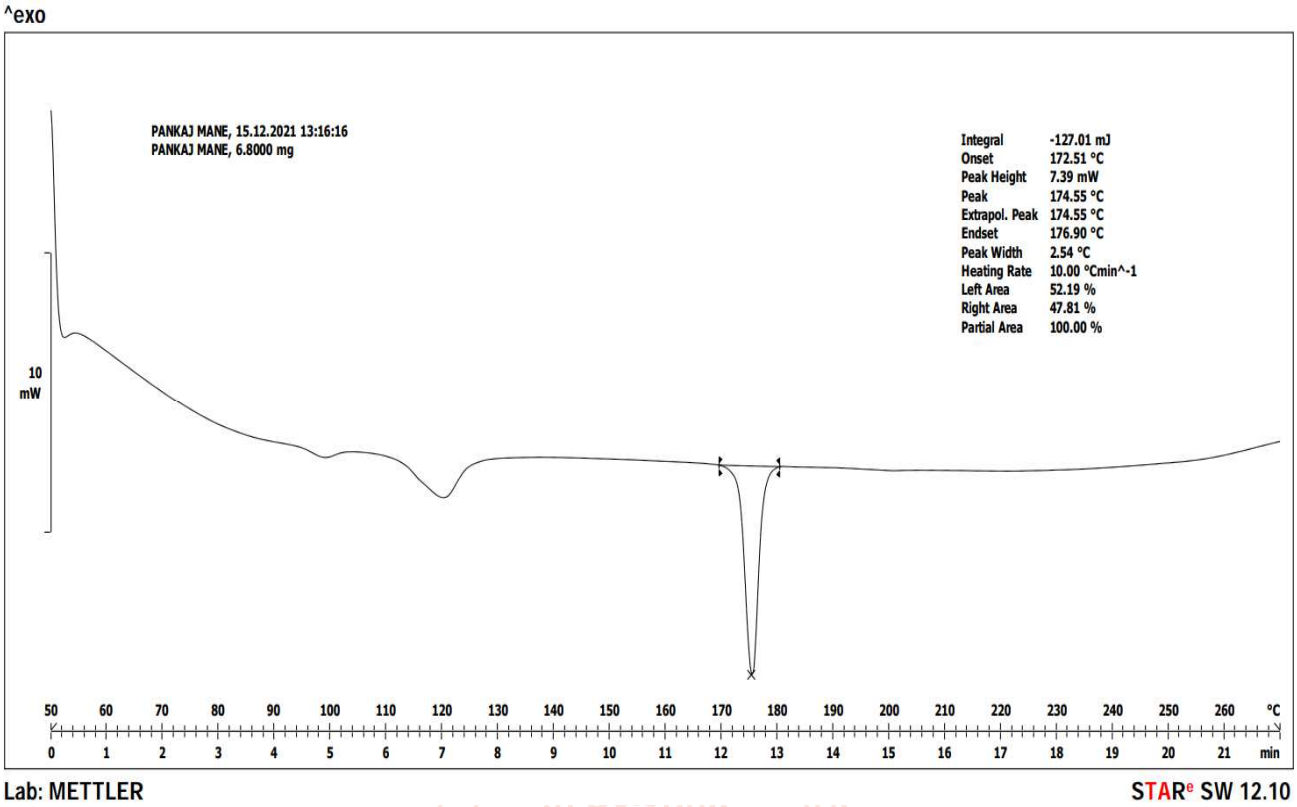

Fig.10 DSC Thermogram of Nifedipine + HPMC E4M and other excipients

Formulation of tablet:

Formulation of tablet blend for Tablet of IR Pioglitazone HCl and SR Nifedipine. The tablet blends for different batch formulation (FP1-FP4) and (FN1-FN4) are prepared And further studied for Pre-compression properties and subjected for tablet punching by direct compression.

Table.1 Formulation of Immediate Release layer of Pioglitazone HCl

Formulations	FP1	FP2	FP3	FP4
Ingredients	Unit formula (mg per tablet)			
Pioglitazone HCl	15	15	15	15
Croscarmellose Sodium	10	15	20	25
Magnesium stearate	2	2	2	2
Talc	8	8	8	8
Microcrystalline cellulose	65	60	55	50
Total	**100**	**100**	**100**	**100**

Table 2 Formulation of Sustained Release Nifedipine Layer

Formulations	FN1	FN2	FN3	FN4
Ingredients	Unit formula (mg per tablet)			
Nifedipine	10	10	10	10
HPMC E4M	25	20	15	10
Magnesium stearate	2	2	2	2
Talc	8	8	8	8
Microcrystalline cellulose	155	160	165	170
Total	**200**	**200**	**200**	**200**

Results:

Precompression study:

Evaluation of prepared tablet blends for pre compression study:

The mass-volume relationship characteristics of a mixed blend were determined by characterization. Angle of repose, bulk density, and tapped density were all examined, with Hauser's ratio and compressibility index given in **Table.3 and Table.4**

Table.3 Evaluation of Powder Blend Pioglitazone HCl

Batch	Angle of Repose (θ˚)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Index (%)
FP1	22.32 ± 0.6	0.432 ± 0.007	0.475 ± 0.008	1.09 ± 0.02	9.52 ± 0.40
FP2	20.55 ± 0.4	0.450 ± 0.003	0.503 ± 0.005	1.11 ± 0.03	10.53 ± 0.30
FP3	22.91 ± 0.1	0.430 ± 0.004	0.497 ± 0.006	1.15 ± 0.01	13.48 ± 0.20
FP4	24.64 ± 0.7	0.449 ± 0.009	0.510 ± 0.004	1.13 ± 0.04	11.96 ± 0.44

Results are mean of three determinations

Table.4 Evaluation of Powder Blend of Nifedipine

Batch	Angle of Repose (θ˚)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Index (%)
FN1	24.07 ±0.4	0.310 ± 0.06	0.351 ± 0.004	1.13 ± 0.08	11.77 ± 0.90
FN2	23.35 ±0.3	0.329 ± 0.04	0.377 ± 0.010	1.14 ± 0.06	12.68 ± 0.32
FN3	23.67 ±0.3	0.351 ± 0.03	0.405 ± 0.007	1.15 ± 0.01	13.31 ± 0.48
FN4	23.54 ±0.1	0.462 ± 0.07	0.524 ± 0.008	1.13 ± 0.04	11.83 ± 15

Results are mean of three determinations

Evaluation of Tablets:

The prepared tablets subjected for weight variation, thickness, hardness, friability, drug content, In-vitro disintegrating time, In-vitro dissolution studies, Assay were carried out.

Table.5 Evaluation of tablets

Batch	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	%Friability (w/w)
F1	299.24 ± 1.12	4.3 ± 0.02	6.2 ± 0.3	0.40 ± 0.035
F2	298.39 ± 1.18	4.2 ± 0.03	6.0 ± 0.1	0.46 ± 0.046
F3	299.50 ± 1.14	4.4 ± 0.08	5.9 ± 0.4	0.49 ± 0.048
F4	299.36 ± 1.54	4.1 ± 0.09	6.1 ± 0.5	0.41 ± 0.023

Results are mean of three determinations

These table show the results of batches of F1-F4 IR Pioglitazone HCl and SR Nifedipine

Table.6 Disintegration Time of Pioglitazone HCl Immediate Release Layer

Formulations	Disintegration time (IR)
F1	70 Sec
F2	92 Sec
F3	88 Sec
F4	98 Sec

Dissolution Study:

All of the formulated tablets were subjected to In vitro dissolution using the USP II Paddle technique at 50 rpm in 0.1 N HCl for the first 2 hours and 6.8 pH buffer solution for the remaining 10 hours. The temperature of the dissolving media was kept constant at 37°C. For Immediate release layer sample extracted after 5,10,15,30,45,60 minutes and for sustained release layer After 1, 2, 4, 8, and 12 hours, 1 ml of the sample was extracted. To keep the volume consistent throughout the experiment, 1 ml of 0.1 N HCl and 6.8 pH buffer solution was employed. The samples were appropriately diluted, and the percentage of drug release from each formulation was determined using a UV-Spectrophotometer at 238 nm and 268 nm.

Table.7 Dissolution study of Immediate Release Layer of Pioglitazone HCl

Time (Min)	FP1 (%)	FP2 (%)	FP3 (%)	FP4 (%)
0	0	0	0	0
5	6.25 ± 0.12	8.843 ± 0.25	9.98 ± 0.32	12.44 ± 0.51
10	24.84 ± 0.31	34.05 ± 0.65	37.65 ± 0.78	39.85 ± 0.36
15	43.90 ± 0.63	48.52 ± 0.52	52.93 ± 0.55	56.21 ± 0.62
30	68.42 ± 0.52	71.98 ± 0.33	76.57 ± 0.44	79.92 ± 0.47
45	80.48 ± 0.11	83.93 ± 0.98	87.09 ± 0.21	89.99 ± 0.34
60	94.19 ± 0.28	96.18 ± 0.17	96.99 ± 0.16	98.89 ± 0.22

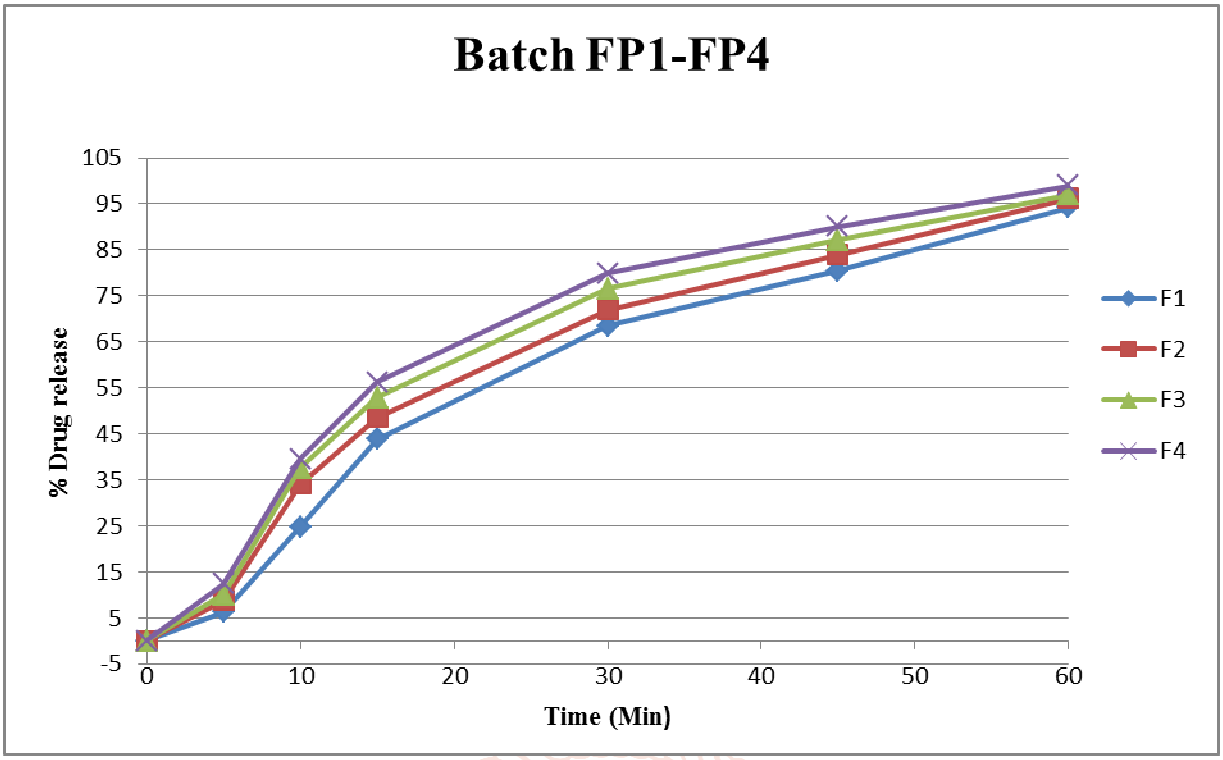

Fig.11 Cumulative Dissolution study of Batch FP1 to FP4

Table.8 Dissolution Study of Sustained Release Layer of Nifedipine

Time (Hour)	FN1 (%)	FN2 (%)	FN3 (%)	FN4 (%)
0	0	0	0	0
1	10.44 ± 0.54	13.73 ± 0.65	15.66 ± 0.28	17.99 ± 0.11
2	24.21 ± 0.25	29.86 ± 0.56	32.12 ± 0.11	36.60 ± 0.74
4	40.38 ± 0.34	47.59 ± 0.94	51.89 ± 0.61	55.98 ± 0.29
8	68.84 ± 0.39	75.88 ± 0.43	80.22 ± 0.22	89.04 ± 0.32
12	84.92 ± 0.21	89.21 ± 0.18	93.83 ± 0.14	98.94 ± 0.37

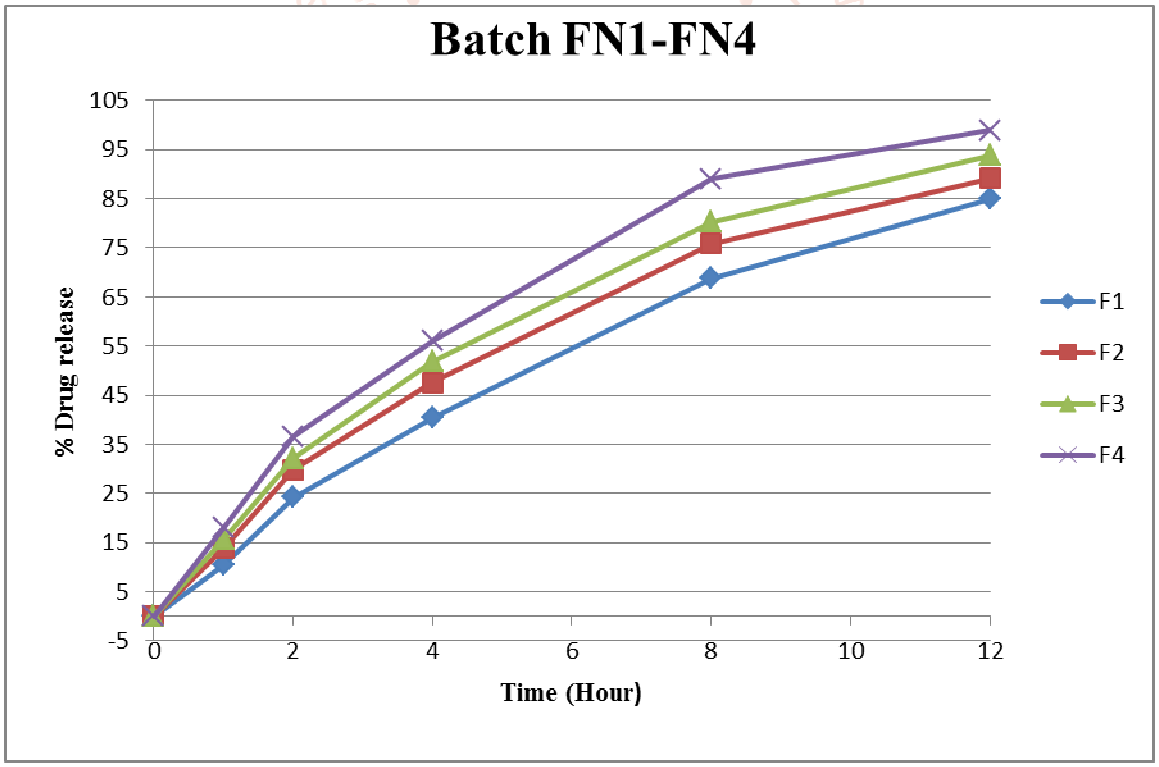

Fig.12 Cumulative Dissolution study of Batch FN1 to FN4

The formulation F4 as an optimized formulation because of these batch showed satisfactory result of the tablets parameter. Result of in vitro % drug release profile an indicated that formulation (F4) was the most promising formulations as the drug release from this formulation was high as compared to other formulations.

Assay:
% Assay of Selected Formulation Batch F4 for Pioglitazone HCl is **100.2 %** and for Nifedipine is **100.7 %**

Stability study:
Stability study for the developed formulation F4 were carried out as per ICH guideline by storing at 40°C/75% RH up to three months. The formulation F4 was selected on the basis of their high cumulative percentage drug release.

Table.9 Stability Study of Optimized Batch F4

Sr. No.	Parameter	Initial	After three months
01	Hardness	4.5	4.5
02	Friability	0.61%	0.58%
03	Disintegration Time (IR layer)	98 Sec.	96 Sec.
04	% Drug Release	98.295±0.09% (FP4) &98.645±0.1% (FN4)	98.145±0.05 (FP4) & 98.573±0.07(FN4)
05	% Assay	100.2±0.12 (FP4) & 100.7±0.2(FN4)	100.1±0.1 (FP4) & 100.5±0.07 (FN4)

The stability study showed that the formulation F4 was physically stable when stored at 40±20°C and 75±5% RH for three months and there was no significant difference in dissolution parameters of optimized formulation.

Conclusion:
Physiochemical characteristics were used to assess the prepared tablet. The physiochemical analysis of the tablet reveals a pale yellow, white color, a round form, and a smooth look. The formulation F4 as an optimized formulation because of these batches showed satisfactory result of the tablets parameter. Result of in vitro % drug release profile an indicated that formulation (F4) was the most promising formulations as the drug release from this formulation was high as compared to other formulations. So, F4 was found to be optimized formulation and was selected for further % assay, stability study. Also, Stability study and % assay of optimized batch is showed satisfactory result.

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